

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number : 10/580,248 Confirmation No.: 6084
Applicant : Mimi ADACHI, *et al.*
35 U.S.C. § 371 Date : July 20, 2006
Title : METHOD FOR PROLIFERATING CARDIOMYOCYTES
TC/Art Unit : 1632
Examiner: : Magdalene K. Sgagias
Docket No. : 64517.000003
Customer No. : 21967

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Commissioner for Patents
P.O. Box 1450
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Pre-Appeal Brief Request for Review

Sir:

Applicants hereby request a pre-appeal conference in the above-identified application. The following responds to the Final Office Action mailed December 22, 2008 (“Office Action”), rejecting claims 1, 2, 4-12, 15-25, 31, 34, and 35. A Notice of Appeal is being filed concurrently herewith.

I. Introduction

Claim 1 is directed to a method for proliferating cardiomyocytes comprising introducing (a) a cyclin, (b) a cyclin-dependent kinase, and (c) a gene encoding a factor that inhibits the production, function, or action of a Cip/Kip family protein, into cardiomyocytes *in vitro*, and subsequently culturing or maintaining said cells.

Claims 1, 2, 4-12, 15-25, and 31 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Adachi in view of Sutterlüty, Sherr, Flink, and Poolman (“the secondary references”).¹ The Examiner asserts that Adachi teaches claim 1, elements (a) and (b), but does not teach “the introduction of a gene encoding a factor that inhibits the production or

¹ The full citations of these references are set forth in Applicants’ Supplemental response, filed October 10, 2008.

function of Cip/Kip family proteins into cardiomyocyte cultures.”² The Examiner contends, however, that it would have been obvious to introduce such a gene into Adachi’s system in view of the secondary references.

Applicants respectfully submit that the obviousness rejection contains at least two errors. First, the secondary references do not teach or suggest claim 1, element (c), i.e., introducing a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein into cardiomyocytes *in vitro*. Second, even if these references did teach element (c), the evidence of record demonstrates that the introduction of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip protein does not result in the proliferation of cardiomyocytes. As such, one of ordinary skill in the art would have had absolutely no reason to combine the teachings of the secondary references with Adachi.

II. The Combination Of References Does Not Render The Claims Obvious

A. The references do not teach or suggest claim 1, element (c)

Claim 1 requires introducing a gene encoding a factor that inhibits the production or function of a Cip/Kip protein into a cardiomyocyte *in vitro*. As discussed below, the secondary references do not, alone or in combination, teach or suggest this element.

1. Sutterlüty

Sutterlüty relates to cell-cycle mechanisms in fibroblasts—actively dividing cells that are physiologically distinct from cardiomyocytes. Sutterlüty does not discuss or provide any teaching whatsoever with respect to cardiomyocytes or methods of proliferating cardiomyocytes. Accordingly, Sutterlüty is unrelated to the claimed invention.

2. Sherr

The Examiner cites Sherr for the proposition that “p27^{kip1} degradation is required for cells to progress through the late G1 phase to the S phase.”³ But Sherr, like Sutterlüty, is also silent with respect to cardiomyocytes and methods of proliferating cardiomyocytes. Moreover, Sherr does not teach or suggest introducing a gene encoding a factor to inhibit production or function of a Cip/Kip protein. Rather, Sherr teaches that an active CDK2

² Non-Final Office Action mailed January 28, 2008, page 4.

³ Office Action, page 5.

triggers the destruction of p27^{Kip1}.⁴ Accordingly, Sherr, like Sutterlüty, is unrelated to the claimed invention.

3. Flink

According to the Examiner, “Flink by teaching that in differentiated cardiomyocytes p27 is increased, this is sufficient motivation for one of skill in the art of cell cycle regulation to degrade p27 in the cardiomyocytes of [Adachi].”⁵

Flink provides no such motivation. Flink is a general reference reporting the changes in E2F complexes containing retinoblastoma protein family members and cyclin-dependent kinase inhibitor activities during terminal differentiation of cardiomyocytes. At best, Flink suggests that a paradox exists for p27, where mRNA levels are stable, but protein levels increase. Flink does not, however, discuss or provide any teachings whatsoever regarding the inhibition of Cip or Kip proteins, let alone teach or suggest modes of inhibiting such proteins. Flink is also silent on methods of proliferating cardiomyocytes.

Adachi discloses a novel method of proliferating cardiomyocytes by introducing a cyclin and cyclin-dependent kinase, but is silent with respect to p27. The Examiner has not established a nexus between Flink and Adachi. Accordingly, the Examiner fails to provide any reason why Flink “provides sufficient motivation ... to degrade p27 in the cardiomyocytes of [Adachi].”

4. Poolman

Poolman is limited to the developmental effects of the absence (i.e., the total loss) of p27 in neonatal cardiomyocytes. In particular, Poolman suggests that a genetically engineered mouse *lacking* p27^{kip1} (i.e., p27^{kip1} knockout mouse) showed “prolonged proliferation of cardiac myocytes.”⁶ Poolman does not teach or suggest inhibiting the production or function of a Cip/Kip protein. Indeed, one of ordinary skill in the art would appreciate that the developmental events influenced by the complete absence of p27^{kip1} during development are not identical to inhibiting a Cip/Kip protein. The Examiner acknowledges that Poolman teaches the total loss of p27, but fails to address the distinction

⁴ See Sherr, page 1503, paragraph bridging first and second columns.

⁵ Office Action, page 5.

⁶ Poolman, page 126.

between a knockout mouse and the introduction of a gene encoding a factor to inhibit production or function of a Cip or Kip protein.

5. The Combination of Sutterlüty, Sherr, Flink, and Poolman

The combination of Sutterlüty, Sherr, Flink, and Poolman also does not teach or suggest a method of introducing a gene encoding a factor that inhibits production or function of Cip/Kip protein into cardiomyocytes *in vitro*. Sutterlüty and Sherr do not relate at all to cardiomyocytes or methods of proliferating cardiomyocytes. Flink relates to cardiomyocytes, but is silent with respect to proliferating cardiomyocytes or inhibiting Cip/Kip proteins. Poolman discloses a p27 knockout mouse, but does not teach or suggest introducing an exogenous factor into cardiomyocytes. Accordingly, the combination of references does not teach or suggest claim 1, element (c).

B. There is no reason to combine the teachings of Sutterlüty, Sherr, Flink, and Poolman with Adachi.

The Examiner asserts that the secondary references, in combination, suggest that introducing a gene encoding a factor that inhibits production or function of p27^{kip1} will proliferate cardiomyocytes.⁷ As discussed below, even if the secondary references taught claim 1, element (c), which they do not, introducing a gene encoding a factor that inhibits production or function of a Cip/Kip protein does not result in cardiomyocyte proliferation.

Indeed, the specification discloses that p27 siRNA-mediated inhibition of p27^{kip1} resulted in virtually no increase in cardiomyocyte cell number.⁸ Accordingly, there is no basis for the Examiner's obviousness rejection.

Nonetheless, the Examiner asserts that the combination of references provides "sufficient motivation for one of ordinary skill in the art to introduce a gene encoding a factor that inhibits production or function of p27^{kip1} to the cardiomyocyte system" of Adachi.⁹

⁷ Non-Final Office Action mailed January 28, 2008, page 6 ("The combination of Sutterlüty, Sherr, Flink, and Poolman suggest the role of p27^{kip1} in cell cycle regulation for the cells to progress from the G1 to S phase and the role of p27^{kip1} in terminal differentiation of cardiomyocytes while its loss is associated with cardiomyocyte cell proliferation.").

⁸ See Specification, Example 5 and Figures 9 and 10; see also page 82, lines 8-11 ("Almost no increase of the cell numbers of cardiomyocytes infected with ... Ad-p27 siRNA alone as negative controls was observed.").

⁹ Non-Final Office Action mailed January 28, 2008, page 6


Applicants respectfully disagree. Since the introduction of p27 siRNA—a factor that inhibits production or function of p27^{kip1}—does not result in the proliferation of cardiomyocytes, one of ordinary skill in the art would have had absolutely no reason or motivation to introduce this factor into Adachi's system.

In view of the foregoing, Applicants respectfully request withdrawal of the obviousness rejection.

CONCLUSION

Applicants respectfully submit that the rejection of claims 1, 4-12, 15-25, 31, 34, and 35 under 35 U.S.C. § 103 (a) is in error and the application is in condition for allowance. Applicants respectfully request withdrawal of this rejection and issuance of a Notice of Allowance.

Respectfully submitted,
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